

## Referral Bias in the Diagnostic Performance of Exercise Testing with Imaging for Coronary Artery Disease

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**Authors:** Joseph A. Ladapo, Saul Blecker, New York University School of Medicine, New York, NY; Michael R. Elashoff, CardioDx, Inc., Palo Alto, CA; Jerome J. Federspiel, Duke University, Durham, NC; Mark Monane, Steven Rosenberg, CardioDx, Inc., Palo Alto, CA; Charles E. Phelps, University of Rochester, Gualala, CA; Pamela S. Douglas, Duke University, Durham, NC

**Purpose:** Exercise testing with myocardial perfusion imaging (MPI) or echocardiography (ECHO) is widely used to risk-stratify patients with suspected coronary artery disease (CAD). However, reports of diagnostic performance do not routinely adjust for referral bias, which results from the preferential referral of higher-risk patients to cardiac catheterization, the gold standard. To understand how this practice may impact test characteristics and clinical decision-making, we systematically reviewed the literature on catheterization referral rates and estimated adjusted measures of diagnostic performance.

**Method:** We searched PubMed and EMBASE for studies reporting catheterization referral rates after normal or abnormal exercise MPI and ECHO. Findings were pooled with the Mantel-Haenszel fixed-effects model, and we used Bayesian methods developed by Begg and Greenes (Biometrics, 1993) to adjust exercise test diagnostic performance reported in a widely cited meta-analysis (Fleischmann et al, JAMA 1998). To evaluate the impact of referral bias on overall diagnostic performance, we constructed summary receiver operating characteristic (SROC) curves and calculated positive and negative predictive values over a range of pretest probabilities.

**Result:** Our literature search yielded 253 citations, of which 10 reported referral patterns in 16,799 patients. Mean age was 60.5 years, 40.3% were women, and 8% had prior history of myocardial infarction. Catheterization referral rates after normal and abnormal exercise tests were 2.3% (95% CI, 2.0%-2.6%) and 30.2% (95% CI, 29.1%-31.3%), respectively, with an odds-ratio for referral after an abnormal test of 10.5 ( $p < 0.001$ ) (Figure). After adjusting for referral, exercise ECHO sensitivity fell from 85% to 33% and specificity rose from 77% to 99%. Similarly, exercise MPI sensitivity fell from 87% to 36% and specificity rose from 64% to 97%. SROC curve analysis demonstrated that the adjustment for referral reduced overall discriminatory power and diagnostic yield. While positive predictive value generally increased, the negative predictive value of a normal exercise test for intermediate risk patients (CAD pretest probability=25%) fell from approximately 93% to 81% for both imaging tests.

**Conclusion:** Exercise ECHO and MPI have lower diagnostic yield after adjusting for the referral process, and patients with normal test results are at risk for misclassification. Incorporating such adjustments into assessments of exercise test performance not only provides a more accurate evaluation of current and emerging diagnostic technologies, but may also significantly influence clinical decision-making and patient care.

**Reference:** Ladapo JA, Blecker S, Elashoff MR, et al. Referral Bias in the Diagnostic Performance of Exercise Testing With Imaging for Coronary Artery Disease. *Med Decis Making*. 2013;33:B-4.

